NDA 19-715/S-019

Pharmacia & Upjohn Company
Attention: Gregory A. Brier
Regulatory Affairs Manager
0633-298-113
7000 Portage Road
Kalamazoo, MI 49001

SEP 8 2000

Dear Mr. Brier:

Please refer to your supplemental new drug application dated July 18, 2000, received July 21, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dipentum (olsalazine) Capsules.

This supplemental new drug application provides for revision of the ADVERSE REACTIONS section of the package insert to include the following sentence: "In a double-blind, placebo controlled study, increased frequency and severity of diarrhea were reported in patients randomized to olsalazine 500 mg B.I.D. with concomitant pelvic radiation."

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted July 18, 2000).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDAs (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-715/S-019." Approval of this submission by FDA is not required before the labeling is used. Our understanding is that Dipentum is marketed in both 100 and 300 count bottles. Therefore, please ensure that you provide appropriate FPL for both package configurations of Dipentum.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we

request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 3l4.80 and 314.81.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research -

Dipentum®

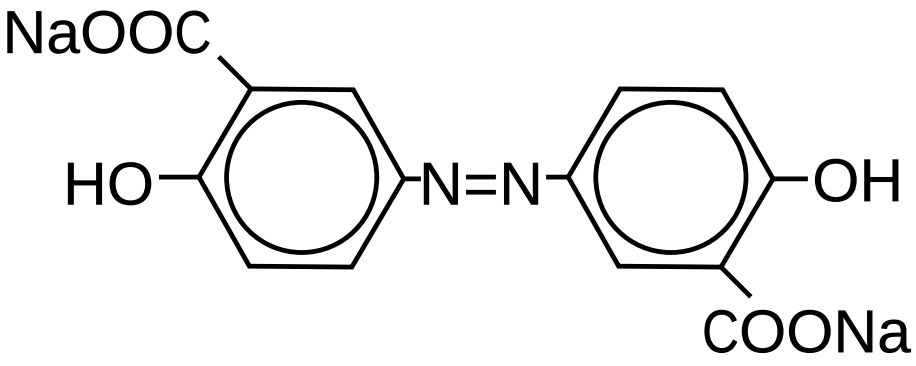
olsalazine sodium capsules

Pharmacia & Upjohn

DESCRIPTION

The active ingredient in DIPENTUM Capsules (olsalazine sodium) is the sodium salt of a salicylate, disodium 3,3'-azobis (6-hydroxybenzoate) a compound that is effectively bioconverted to 5-aminosalicylic acid (5- ASA), which has anti-inflammatory activity in ulcerative colitis. Its empirical formula is $C_{14}H_8N_2Na_2O_6$ with a molecular weight of 346.21.

The structural formula is:



Olsalazine sodium is a yellow crystalline powder which melts with decomposition at 240°C. It is the sodium salt of a weak acid, soluble in water and DMSO, and practically insoluble in ethanol, chloroform and ether. Olsalazine sodium has acceptable stability under acidic or basic conditions.

DIPENTUM is supplied in hard gelatin capsules for oral administration. The inert ingredient in each 250 mg capsule of olsalazine sodium is magnesium stearate. The capsule shell has the following inactive ingredients: black iron oxide, caramel, gelatin, and titanium dioxide.

CLINICAL PHARMACOLOGY

After oral administration, olsalazine has limited systemic bioavailability. Based on oral and intravenous dosing studies, approximately 2.4% of a single 1.0 g oral dose is absorbed. Less than 1% of olsalazine is recovered in the urine. The remaining 98 to 99% of an oral dose will reach the colon where each molecule is rapidly converted into two molecules of 5-aminosalicylic acid (5-ASA) by colonic bacteria and the low prevailing redox potential found in this environment. The liberated 5-ASA is absorbed slowly resulting in very high local concentrations in the colon.

The conversion of olsalazine to mesalamine (5-ASA) in the colon is similar to that of sulfasalazine, which is converted into sulfapyridine and mesalamine. It is thought that the mesalamine component is therapeutically active in ulcerative

colitis (A.K. Azad-Kahn et al, *LANCET*, 2: 892-895, 1977). The usual dose of sulfasalazine for maintenance of remission in patients with ulcerative colitis is 2 grams daily, which would provide approximately 0.8 gram of mesalamine to the colon. More than 0.9 gram of mesalamine would usually be made available in the colon from 1 gram of olsalazine.

The mechanism of action of mesalamine (and sulfasalazine) is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs) is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

Pharmacokinetics

The pharmacokinetics of olsalazine are similar in both healthy volunteers and in patients with ulcerative colitis. Maximum serum concentrations of olsalazine appear after approximately 1 hour, and, even after a 1.0 g single dose, are low, e.g., 1.6 to 6.2 μmol/L. Olsalazine has a very short serum half-life, approximately 0.9 hours. Olsalazine is more than 99% bound to plasma proteins. It does not interfere with protein binding of warfarin. The urinary recovery of olsalazine is below 1%.

Total recovery of oral ^{14}C-labeled olsalazine in animals and humans ranges from 90 to 97%.

Approximately 0.1% of an oral dose of olsalazine is metabolized in the liver to olsalazine-O-sulfate (olsalazine-S). Olsalazine-S, in contrast to olsalazine has a half-life of 7 days. Olsalazine-S accumulates to steady state within 2 to 3 weeks.

Patients on daily doses of 1.0 g olsalazine for 2 to 4 years show a stable plasma concentration of olsalazine-S (3.3 to 12.4 μmol/L). Olsalazine-S is more than 99% bound to plasma proteins. Its long half-life is mainly due to slow dissociation from the protein binding site. Less than 1% of both olsalazine and olsalazine-S appears undissociated in plasma.

5-aminosalicylic acid (5-ASA): Serum concentrations of 5-ASA are detected after 4 to 8 hours. The peak levels of 5-ASA after an oral dose of 1.0 g olsalazine are low, i.e., 0 to 4.3 μmol/L. Of the total 5-ASA found in the urine, more than 90% is in the form of N-acetyl-5-ASA (Ac-5-ASA). Only small amounts of 5-ASA are detected.

N-acetyl-5-ASA (Ac-5-ASA), the major metabolite of 5-ASA found in plasma and urine, is acetylated (deactivated) in at least two sites, the colonic epithelium and the liver. Ac-5-ASA is found in the serum, with peak values of

1.7 to 8.7 μmol/L after a single 1.0 g dose. Approximately 20% of the total 5-ASA is recovered in the urine, where it is found almost exclusively as Ac-5-ASA. The remaining 5-ASA is partially acetylated and is excreted in the feces. From fecal dialysis, the concentration of 5-ASA in the colon following olsalazine has been calculated to be 18 to 49 mmol/L. No accumulation of 5-ASA or Ac-5-ASA in plasma has been detected. 5-ASA and Ac-5-ASA are 74 and 81%, respectively, bound to plasma proteins.

ANIMAL TOXICOLOGY

Preclinical subacute and chronic toxicity studies in rats have shown the kidney to be the major target organ of olsalazine toxicity. At an oral daily dose of 400 mg/kg or higher, olsalazine treatment produced nephritis and tubular necrosis in a 4-week study; interstitial nephritis and tubular calcinosis in a 6-month study, and renal fibrosis, mineralization and transitional cell hyperplasia in a 1-year study.

CLINICAL STUDIES

Two controlled studies have demonstrated the efficacy of olsalazine as maintenance therapy in patients with ulcerative colitis. In the first, ulcerative colitis patients in remission were randomized to olsalazine 500 mg B.I.D. or placebo, and relapse rates for a six month period of time were compared. For the 52 patients randomized to olsalazine, 12 relapses occurred, while for the 49 placebo patients, 22 relapses occurred. This difference in relapse rates was significant ($p<.02$).

In the second study, 164 ulcerative colitis patients in remission were randomized to olsalazine 500 mg B.I.D. or sulfasalazine 1 gram B.I.D., and relapse rates were compared after six months. The relapse rate for olsalazine was 19.5% while that for sulfasalazine was 12.2%, a non-significant difference.

INDICATIONS AND USAGE

Olsalazine is indicated for the maintenance of remission of ulcerative colitis in patients who are intolerant of sulfasalazine.

CONTRAINDICATIONS

Hypersensitivity to salicylates.

PRECAUTIONS

General

Overall, approximately 17% of subjects receiving olsalazine in clinical studies reported diarrhea sometime during therapy. This diarrhea resulted in withdrawal of treatment in 6% of patients. This diarrhea appears to be dose related, although it may be difficult to distinguish from the underlying symptoms of the disease.

Exacerbation of the symptoms of colitis thought to have been caused by mesalamine or sulfasalazine has been noted.

Although renal abnormalities were not reported in clinical trials with olsalazine, there have been rare reports from

post-marketing experience (see under ADVERSE REACTIONS). Therefore, the possibility of renal tubular damage due to absorbed mesalamine or its n-acetylated metabolite, as noted in the ANIMAL TOXICOLOGY section must be kept in mind, particularly for patients with pre-existing renal disease. In these patients, monitoring with urinalysis, BUN and creatinine determinations is advised.

Information for Patients

Patients should be instructed to take olsalazine with food. The drug should be taken in evenly divided doses. Patients should be informed that about 17% of subjects receiving olsalazine during clinical studies reported diarrhea sometime during therapy. If diarrhea occurs, patients should contact their physician.

Drug Interactions: Increased prothrombin time in patients taking concomitant warfarin has been reported.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two year oral rat carcinogenicity study, olsalazine was tested in male and female Wistar rats at daily doses of 200, 400 and 800 mg/kg/day (approximately 10 to 40 times the human maintenance dose, based on a patient weight of 50 kg and a human dose of 1 g). Urinary bladder transitional cell carcinomas were found in three male rats (6%, p=0.022,

exact trend test) receiving 40 times the human dose and were not found in untreated male controls. In the same study, urinary bladder transitional cell carcinoma and papilloma occurred in 2 untreated control female rats (2%). No such tumors were found in any of the female rats treated at doses up to 40 times the human dose.

In an eighteen month oral mouse carcinogenicity study, olsalazine was tested in male and female CD-1 mice at daily doses of 500, 1000 and 2000 mg/kg/day (approximately 25 to 100 times the human maintenance dose). Liver hemangiosarcomata were found in two male mice (4%) receiving olsalazine at 100 times the human dose, while no such tumor occurred in the other treated male mice groups or any of the treated female mice. The observed incidence of this tumor is within the 4% incidence in historical controls.

Olsalazine was not mutagenic in *in vitro* Ames tests, mouse lymphoma cell mutation assays, human lymphocyte chromosomal aberration tests and the *in vivo* rat bone marrow cell chromosomal aberration test.

Olsalazine in a dose range of 100 to 400 mg/kg/day (approximately 5 to 20 times the human maintenance dose) did not influence the fertility of male or female rats. The oligospermia and infertility in men associated with sulfasalazine have not been reported with olsalazine.

Pregnancy. Teratogenic Effects. Pregnancy Category C.
Olsalazine has been shown to produce fetal developmental toxicity as indicated by reduced fetal weights, retarded ossifications and immaturity of the fetal visceral organs when given during organogenesis to pregnant rats in doses 5 to 20 times the human dose (100 to 400 mg/kg). There are no adequate and well-controlled studies in pregnant women. Olsalazine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Oral administration of olsalazine to lactating rats in doses 5 to 20 times the human dose produced growth retardation in their pups. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when olsalazine is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in a pediatric population have not been established.

ADVERSE REACTIONS

Olsalazine has been evaluated in ulcerative colitis patients in remission as well as those with acute disease. Both sulfasalazine-tolerant and intolerant patients have been studied in controlled clinical trials. Overall, 10.4% of patients discontinued olsalazine because of an adverse experience

compared with 6.7% of placebo patients. The most commonly reported adverse reactions leading to treatment withdrawal were diarrhea or loose stools (olsalazine 5.9%; placebo 4.8%), abdominal pain and rash or itching (slightly more than 1% of patients receiving olsalazine). Other adverse reactions to olsalazine leading to withdrawal occurred in fewer than 1% of patients (TABLE 1).

TABLE 1
Adverse Reactions Resulting in Withdrawal From Controlled Studies

	Total	
	Olsalazine (N = 441)	Placebo (N = 208)
Diarrhea/ Loose Stools	26 (5.9%)	10 (4.8%)
Nausea	3	2
Abdominal Pain	5 (1.1%)	0
Rash/Itching	5 (1.1%)	0
Headache	3	0
Heartburn	2	0
Rectal Bleeding	1	0
Insomnia	1	0
Dizziness	1	0
Anorexia	1	0
Light Headedness	1	0
Depression	1	0
Miscellaneous	4 (0.9%)	3 (1.4%)
Total Number of Patients Withdrawn	46 (10.4%)	14 (6.7%)

For those controlled studies, the comparative incidences of adverse reactions reported in 1% or more patients treated with olsalazine or placebo are provided in TABLE 2.

TABLE 2: COMPARATIVE INCIDENCE (%) OF ADVERSE EFFECTS REPORTED BY ONE PERCENT OR MORE OF ULCERATIVE COLITIS PATIENTS TREATED WITH OLSALAZINE OR PLACEBO IN DOUBLE BLIND CONTROLLED STUDIES

	Olsalazine (N = 441) %	Placebo (N = 208) %
ADVERSE EVENT		
Digestive System		
Diarrhea	11.1	6.7
Abdominal Pain/ Cramps	10.1	7.2
Nausea	5.0	3.9
Dyspepsia	4.0	4.3
Bloating	1.5	1.4
Anorexia	1.3	1.9
Vomiting	1.0	-
Stomatitis	1.0	-
Increased Blood in Stool	-	3.4
CNS/Psychiatric		
Headache	5.0	4.8
Fatigue/Drowsiness/ Lethargy	1.8	2.9

(TABLE 2, cont.)	Olsalazine %	Placebo %
Depression	1.5	-
Vertigo/Dizziness	1.0	-
Insomnia	-	2.4
Skin		
Rash	2.3	1.4
Itching	1.3	-
Musculoskeletal		
Arthralgia/Joint Pain	4.0	2.9
Miscellaneous		
Upper Respiratory Infection	1.5	-

Over 2,500 patients have been treated with olsalazine in various controlled and uncontrolled clinical studies. In these as well as in the post-marketing experience, olsalazine was administered mainly to patients intolerant to sulfasalazine. There have been rare reports of the following adverse effects in patients receiving olsalazine. These were often difficult to distinguish from possible symptoms of the underlying disease or from the effects of prior and/or concomitant therapy.
A causal relationship to the drug has not been demonstrated for some of these reactions.

Digestive: Pancreatitis, diarrhea with dehydration, increased blood in stool, rectal bleeding, flare in symptoms, rectal discomfort, epigastric discomfort, flatulence.

In a double-blind, placebo-controlled study, increased frequency and severity of diarrhea were reported in patients randomized to olsalazine 500 mg B.I.D. with concomitant pelvic radiation.

Rare cases of granulomatous hepatitis and nonspecific, reactive hepatitis have been reported in patients receiving olsalazine. Additionally, a patient developed mild cholestatic hepatitis during treatment with sulfasalazine and experienced the same symptoms two weeks later after the treatment was changed to olsalazine. Withdrawal of olsalazine led to complete recovery in these cases.

Neurologic: Paresthesia, tremors, insomnia, mood swings, irritability, fever chills, rigors.

Dermatologic: Erythema nodosum, photosensitivity, erythema, hot flashes, alopecia.

Musculoskeletal: Muscle cramps.

Cardiovascular/Pulmonary: Pericarditis, second degree heart block, interstitial pulmonary disease, hypertension, orthostatic hypotension, peripheral edema, chest pains, tachycardia, palpitations, bronchospasm, shortness of breath.

A patient who developed thyroid disease 9 days after starting DIPENTUM was given propranolol and radioactive iodine and subsequently developed shortness of breath and nausea.

The patient died 5 days later with signs and symptoms of acute diffuse myocarditis.

Genitourinary: Frequency, dysuria, hematuria, proteinuria, nephrotic syndrome, interstitial nephritis, impotence, menorrhagia.

Hematologic: Leucopenia, neutropenia, lymphopenia, eosinophilia, thrombocytopenia, anemia, hemolytic anemia, reticulocytosis.

Laboratory: ALT (SGPT) or AST (SGOT) elevated beyond the normal range.

Special Senses: Tinnitus, dry mouth, dry eyes, watery eyes, blurred vision.

Postmarketing Reports

The following events have been identified during post-approval use of products which contain (or are metabolized to) mesalamine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine:
Gastrointestinal: Reports of hepatotoxicity, including elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic

jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. One case of Kawasaki-like syndrome, which included hepatic function changes, was also reported.

DRUG ABUSE AND DEPENDENCY

Abuse: None reported.

Dependence: Drug dependence has not been reported with chronic administration of olsalazine.

OVERDOSAGE

No overdosage has been reported in humans. Maximum single oral doses of 5 g/kg in mice and rats and 2 g/kg in dogs were not lethal. Symptoms of acute toxicity were decreased motor activity and diarrhea in all species tested and in addition, vomiting in dogs.

DOSAGE AND ADMINISTRATION

The usual dosage in adults for maintenance of remission is 1.0 g/day in two divided doses.

HOW SUPPLIED

Beige colored capsules, containing 250 mg olsalazine sodium imprinted with "DIPENTUM® 250 mg" on the capsule shell. Packaged in bottles of 100 (NDC 0013-0105-01) and 300 (NDC 0013-0105-20).

Storage

Store at 25°C (77°F). Excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

℞ only

Manufactured for: Pharmacia & Upjohn Company, Kalamazoo, MI 49001, USA
by: Pharmacia & Upjohn AB, Stockholm, Sweden